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Full Length Article

Assessing the clinical and cost impact of on-demand immunoassay testing for the diagnosis of heparin induced thrombocytopenia

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ABSTRACT

Background: The diagnostic work-up for heparin induced thrombocytopenia (HIT) can take several days. Consequently patients may be speculatively switched onto replacement anticoagulant therapy before a diagnosis is confirmed. On-demand immunoassay diagnostic testing enables timely treatment decisions, based on test results.
Objective: To estimate the clinical and cost impact of the use of on-demand versus batched diagnostic tests for HIT.
Methods: Literature was reviewed to identify test performance, clinical and cost data. Semi-structured interviews (n = 4) and a survey (n = 90) provided insights into current practice and challenges. Flow diagram models were developed to estimate the potential impact of on-demand testing.
Results: Modelling estimated more HIT-related outcomes for patients maintained on heparin whilst awaiting test results and patients switched onto replacement anticoagulant therapy awaiting test results, compared with on-demand testing and treatment based on the results. The budget impact model estimated that on-demand testing reduced replacement anticoagulant therapy costs from $39,616 to $12,799 per patient. There are limitations to the data available to inform modelling and the estimates should be treated with caution.
Conclusions: Using on-demand testing may drive positive effects on clinical and cost outcomes.

1. Introduction

Heparin induced thrombocytopenia (HIT) is a prothrombotic, immune-mediated disorder caused by exposure to heparin [1]. Guidance on the diagnosis and management of HIT [2–4], recommends that patients whose platelet count drops by over 50% within 5–14 days of heparin administration undergo clinical assessment using the 4Ts score [5]. Those with a low score are unlikely to have HIT, while those with high or intermediate score should undergo HIT immunoassay testing. Those with positive immunoassay tests should undergo functional testing to confirm HIT diagnosis. Management of HIT involves cessation of heparin and initiation of alternative parenteral anticoagulants, such as a direct thrombin inhibitor or an indirect factor Xa inhibitor. The two major issues in HIT testing are test performance and test turnaround time [6, 7].

1.1. Test performance

The polyspecific enzyme-linked immunosorbent assay (ELISA IgGAM) is the most commonly used tests for diagnosing HIT. ELISAs have high sensitivity, but poor specificity and positive predictive value. An antibody-specific ELISA targeting IgG antibodies (most frequently implicated in HIT) partly addresses these performance issues [8], however, false positives remain a challenge [7]. Performance issues potentially lead to increased expense as patients are treated unnecessarily using replacement anticoagulant therapy and they may have poorer clinical outcomes if the true cause of their symptoms is not addressed. The gold standard diagnostic test for HIT is the functional serotonin release assay (SRA), which demonstrates higher specificity than ELISAs.

1.2. Test turnaround time

Immunoassay tests take 2–3 h to run, but batching of multiple patient samples into a single run is common, delaying the time-to-result to over 24 h. SRA testing is technically demanding, restricting its use to specialty laboratories [8]. Outsourcing to specialty laboratories is common, with turnaround times of over 24 h and a potential total turnaround time of several days for the diagnostic work-up. The total turnaround time may preclude following the pathway by increasing costs and worsen

Abbreviations: DDD, defined daily dose; DTI, direct thrombin inhibitor; ELISA, enzyme-linked immunosorbent assay; HIT, heparin induced thrombocytopenia; HITT, heparin induced thrombocytopenia with thrombosis; SRA, serotonin release assay; T&SC, test and switch, continue; T&SR, test and switch, return; T&W, test and wait.

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clinical outcomes for people with HIT, as they may develop more serious complications if they are kept on heparin whilst awaiting laboratory confirmation of diagnosis. Therefore patients are often speculatively switched from heparin onto expensive replacement anticoagulant therapy based on the clinical assessment alone [2, 8], increasing drug costs.

The objective of this study was to review currently available assays for the diagnosis of HIT, and investigate the potential clinical and cost impact of on-demand testing. On-demand testing can be achieved using either automated tests such as HemosIL® HIT-Ab(PF4-H) (Instrumentation Laboratory, Bedford, MA), rapid tests such as particle gel immunoassay (PaGIA) and lateral flow immunoassay, as well as ELISA tests when performed on-demand. These options are not currently routinely used in most settings.

2. Materials and methods

2.1. Literature searches

Literature searches were conducted in Medline, Embase, the Cochrane Library and Scopus, to identify studies on the test performance of HIT diagnostics, clinical outcomes and cost data related to the diagnosis and management of HIT. Searches were carried out in the US National Guidelines Clearinghouse to identify relevant guidelines and in trial registries (ClinicalTrials.gov and the International Clinical Trials Registry Platform Search Portal) to identify on-going trials of relevance. A combination of relevant free text keywords and indexing terms (where available) were used to retrieve relevant guidelines, systematic reviews, randomised controlled trials, diagnostic studies and economic evaluations. The last searches were carried out on 25th February 2015 and limited to English language only.

2.2. Primary research

Primary research was conducted to understand real-world practice, as compared with the guideline pathways [2–4] and to identify challenges faced. The first phase was semi-structured interviews with US-based laboratory managers and haemostasis physicians (n = 4), questions were based on emergent themes from the literature review. Interview findings informed a second phase survey (n = 90) in Germany, the UK and US designed to validate the findings from phase one and fill in data gaps identified in the available literature. Primary research participants were recruited via a market research agency (Research Now) and were reimbursed. Informed consent was obtained prior to commencing the interview/survey. Interviews were carried out by telephone and recorded for transcription purposes. Surveys were completed online. Participants were informed about the overall aims of the project, but not that on-demand testing was the focus, to avoid biasing their responses.

2.3. Clinical and cost flow models

To estimate the potential clinical and cost impact of on-demand testing, the flow of a hypothetical cohort of patients through the care pathway was modelled using four scenarios. The first step for each cohort was a 4Ts clinical assessment, indicating high or intermediate score:

- "Test and wait" (T&W) — 4Ts score high or intermediate, antibody test is ordered (to be run in a batch), patient remains on heparin awaiting the results of the batched antibody test.
- "4Ts and switch, continue" (T&SC) — 4Ts score high or intermediate, antibody test is ordered, patient is placed onto replacement anticoagulant based on the 4Ts score. Patients continue replacement therapy regardless of antibody test result.
- "4Ts and switch, return" (T&SR) — 4Ts score high or intermediate, antibody test is ordered, patient is placed onto replacement anticoagulant based on the 4Ts score. Negative antibody test patients switched back to heparin.
- "On-demand and switch" — 4Ts score high or intermediate, on-demand antibody test is ordered, patient is placed onto replacement anticoagulant based on on-demand assay result.

These scenarios built upon previous research [6] and were designed to model the clinical and cost impact of different testing strategies, and test the importance of timely and accurate results in HIT diagnosis. T&W reflects following the guideline pathway and the impact of delayed test results [2–4]. The two 4Ts and switch using batched IgGAM scenarios represent speculatively switching based on clinical assessment alone, because half of survey respondents indicated that they do so. The on-demand scenario compared settings where test results are available on-demand. The on-demand scenario does not apply to the majority of settings, as the survey indicated that ELISA tests are often batched and results are not available on-demand. Fig. 1 provides an overview of the different scenarios.

Initially a different set of scenarios was used: T&W, a single "4Ts and switch" and separate "on-demand and switch" scenarios for HemosIL, IgG and IgGAM. However, the data from the survey indicated that a large proportion of patients are not switched back to heparin, even when test results indicate that they are HIT-negative. Therefore the decision was taken to change the scenarios to reflect these findings, in order to produce an analysis that was more representative of real practice. The most pronounced difference in the scenarios in terms of clinical outcomes was between the batched and on-demand scenarios, rather than between the different tests used on-demand. Given the limitations to the data available, the small difference seen between the on-demand tests (2 cases of new thrombosis) may not be reliable. Therefore results were grouped for the different on-demand tests.

Within each scenario, four diagnostic groups were established – true negatives, false positives, true positives, false negatives – based on the performance of the 4Ts clinical assessment reported in the literature. The prevalence of HIT varied across the included studies, making it difficult to compare their results, therefore a normalised frequency representation for prevalence was calculated. Prevalence for normalisation was based on median HIT prevalence (confirmed clinically or by SRA testing) in the included studies, and the median sensitivity and specificity of each class of diagnostic assay was used to calculate the false positive rate (1 — Specificity) and false negative rate (1 — Sensitivity). This approach enabled the calculation of the impact of each scenario on the hypothetical cohort by making the input data comparable. This approach is based on the methodology recommended by the Cochrane Collaboration for comparing diagnostic accuracy studies [9]. The normalised HIT prevalence was 20.4%.

Assay performance data for the flow models was derived from the identified literature comparing the index test (4Ts clinical assessment, HemosIL® HIT-Ab(PF4-H), ELISA IgG, ELISA IgGAM) to either clinical HIT or the gold standard SRA (see Table 1).

The treatment strategies included in each scenario assumed the following:

- True negatives continued to receive heparin.
- False positives were unnecessarily switched to a replacement anticoagulant therapy (argatroban, bivalirudin, danaparoid, fondaparinux, lepirudin) according to country-specific guidance.
- False negatives with isolated HIT continued to receive heparin, while those with HIT with thrombosis (HITT) were switched to replacement anticoagulant therapy.
- True positives in the T&S and on-demand scenarios were given replacement anticoagulant therapy. In T&W scenario, only HITT patients were treated early, and HIT patients were treated late, after the results of an ELISA IgGAM (the most common test) were obtained.

2.3.1. Clinical outcomes representing HIT complications

Clinical outcomes were defined as the aggregate of clinical outcomes representing HIT complications: new thrombosis, bleeding events and deaths. These were compared across the diagnostic groups for each